00330-2

CSF and Plasma Biomarker Changes After Anti-Tau Therapy: Fluid Biomarker Results from the Autonomy Phase 2 Clinical Trial

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*Presenting author

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This study was sponsored by Johnson & Johnson

Disclosures

- **Gallen Triana-Baltzer, Tina Wang, Shannon Leslie, Manja Schoene, Setareh Moughadam, Antoella Scaglione, Ziad S. Saad, Janice Wong, Stanley Belkowski, Gayle Wittenberg, Tricia Thornton-Wells, Maggie Fedgchin, Arthur Simen, and Fiona Elwood:** Are employees of Johnson & Johnson and may hold stock or stock options in Johnson & Johnson.
- **Gil D. Rabinovici:** receives research support from NIH, Alzheimer's Association, American College of Radiology, Rainwater Charitable Foundation, Eli Lilly, GE Healthcare, Life Molecular Imaging, Genentech. Paid consultant for Bristol Myers Squibb, Eli Lilly, Genentech, Johnson & Johnson, Merck, Novo Nordisk, Roche.
- **Reisa Sperling:** has served as a consultant or on scientific advisory boards for AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Immunobrain, Janssen, Novo Nordisk, Oligomerix, Prothena, Roche, Ionis, Therini and Vaxxinity over the past 3 years, all under the NIH guidelines of $5k. She also has institutional consulting contracts with Eli Lilly and Roche. She has received research funding from Eisai and Eli Lilly for public-private partnership clinical trials and receives research grant funding from the National Institute on Aging/National Institutes of Health, GHR Foundation, and the Alzheimer's Association. Her spouse, K. Johnson, reports consulting fees from Bristol-Myers Squibb, Janssen, Merck, Novartis and Voyager Therapeutics over the past 3 years.
- **Henrik Zetterberg:** has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alamar, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, Johnson & Johnson, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, New Amsterdam, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work).

Presented by Gallen Triana-Baltzer at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Background: Testing mechanistic hypotheses about extracellular tau requires interventional studies

- CSF and plasma biomarkers profiled in longitudinal observational cohorts (e.g., ADNI, AIBL, DIAN) have defined models of tau pathology progression and cognitive decline in AD
- Testing mechanistic hypotheses, particularly regarding extracellular tau and its role in propagation, requires interventional studies integrating extensive biomarker measurements and clinical endpoints
- Autonomy was a randomized, placebo-controlled Phase 2 study of posdinemab (JNJ-63733657), an anti-tau IgG1 mAb, in MCI or mild dementia due to AD, with biomarker-driven enrollment, longitudinal ^{18}F-MK-6240 tau PET and serial fluid (plasma and CSF) biomarkers[1]
- Previously reported: Posdinemab was not superior to placebo on the primary endpoint (iADRS-MCI; $p>0.05$) or secondary endpoints; tau PET effects were modest and regionally restricted (e.g., 26% slowing at week 104 in inferior temporal cortex, nominal $p<0.05$)[2,3]

Autonomy: Frequency of cognition, tau PET, and CSF and plasma biomarker collection

Assessment/sample collection	Week 0	Week 12	Week 24	Week 36	Week 52	Week 76	Week 104
Cognition (e.g. ADAS-Cog)	x		x		x	x	x
TauPET	x				x		x
CSF (optional)	x				x		x
plasma	x	x	x	x	x	x	x

1. ClinicalTrials.gov. NCT04619420. Accessed October 2026. 2. Cohen S, et al. Presented at: AD/PD 2026; March 17-21, 2026; Copenhagen, Denmark. 3. Saad ZS, et al. Presented at: AAIC 2026; July 12-15, 2026; London, UK.
AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale; CSF, cerebrospinal fluid; iADRS, integrated Alzheimer's Disease Rating Scale; mAb, monoclonal antibody; MCI, mild cognitive impairment; PET, positron emission tomography; IgG1, immunoglobulin G1.

Objective

- To report longitudinal fluid biomarker changes during 2-year treatment with posdinemab in Autonomy:
  - Tau biomarkers: tTau, p-tau181, p-tau205, p-tau217, p-tau231, eMTBR243
  - Synaptic, neuronal and inflammation biomarkers: NfL, GFAP, SNAP25, βSyn, NRGN, NULISA panels
  - Describe which biomarkers indicate target engagement versus pharmacodynamic impacts

βSyn, β-synuclein; eMTBR, endogenous microtubule-binding region; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; NRGN, neurogranin; NULISA, nucleic acid-linked immuno-sandwich assay; p-tau, phosphorylated tau; SNAP25, synaptosomal-associated protein 25; tTau, total tau.

Presented by Gallen Triana-Baltzer at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Methods: Autonomy used a battery of robust CSF and plasma biomarkers as exploratory endpoints

Due to the proof-of-concept nature of anti-tau treatment and the recent availability of these tools

A diverse set of A-T-N-I markers was measured, probing unique aspects of AD biology

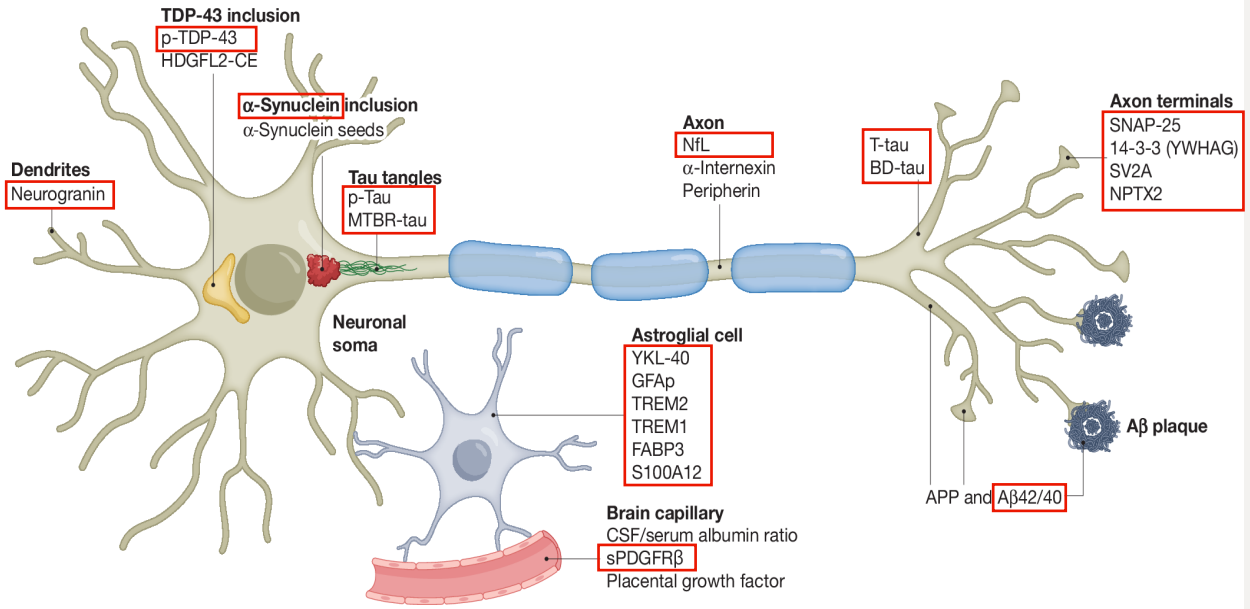
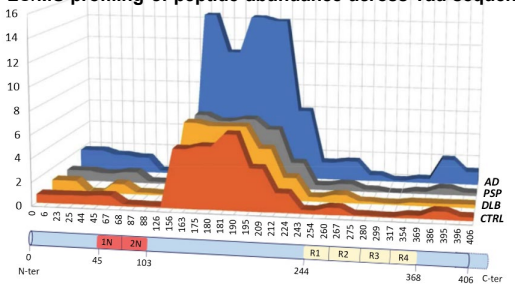


Figure adapted from Zetterberg H, Bendlin BB[1]

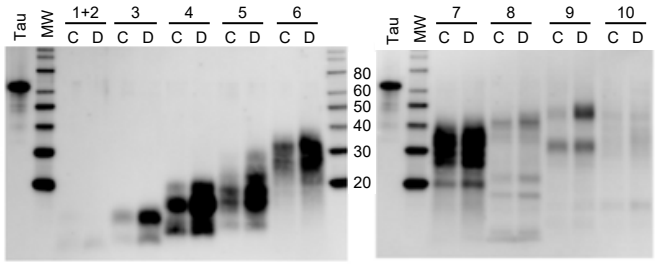
CSF tau complexity: dozens of known cleavage sequences → substantial and heterogeneous fragmentation in fluids

LC/MS profiling of peptide abundance across Tau sequence



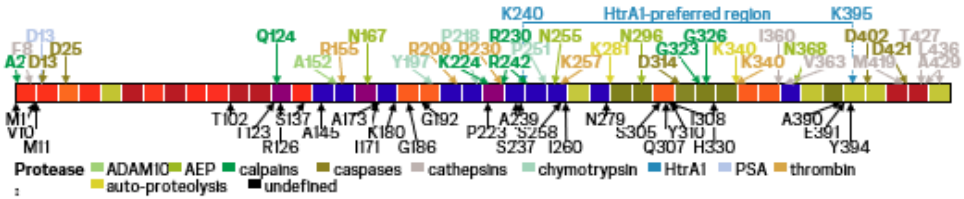
Adapted from Barthélemy NR, et al.[2]

HT7 probing of HPLC fractions



Adapted from Meredith JE Jr, et al.[3]

Numerous known tau cleavage sites



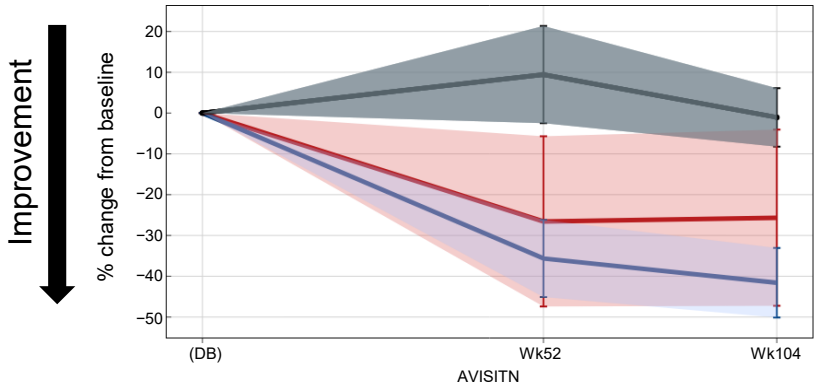
Adapted from Chu D, et al.[4]

Boxed analytes were measured in Autonomy CSF and/or plasma (tTau, p-tau181, p-tau205, p-tau217, p-tau231 and eMTBR243 via Lumipulse, Simoa and/or C2N); a larger set of inflammation and CNS proteins was also profiled with NULISA and SomaScan.

1. Zetterberg H, Bendlin BB. *Nature.* 2026 Feb;650(8100):49-59. 2. Barthélemy NR, et al. *J Alzheimers Dis.* 2016;51(4):1033-1043. 3. Meredith JE Jr, et al. *PLoS One.* 2013 Oct 7;8(10):e76523. 4. Chu D, et al. *Neural Regen Res.* 2024 Jun;19(6):1221-1232.
CNS, central nervous system; CSF, cerebrospinal fluid; eMTBR, endogenous microtubule-binding region; NULISA, nucleic acid-linked immuno-sandwich assay; tTau, total tau.

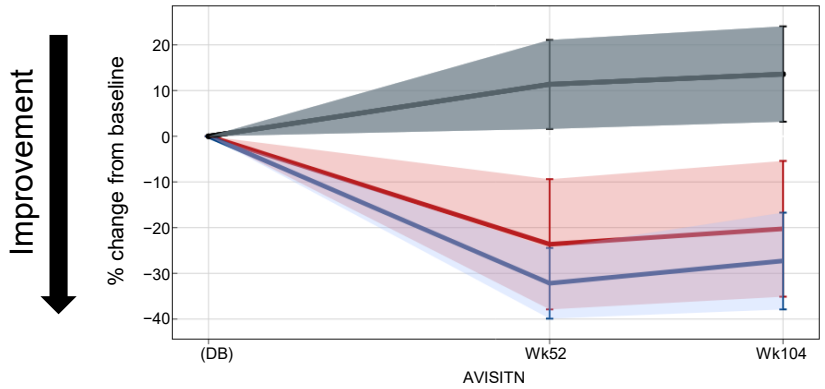
Results: All standard CSF tau biomarkers were reduced by posdinemab

Percent change from baseline in CSF p-tau181



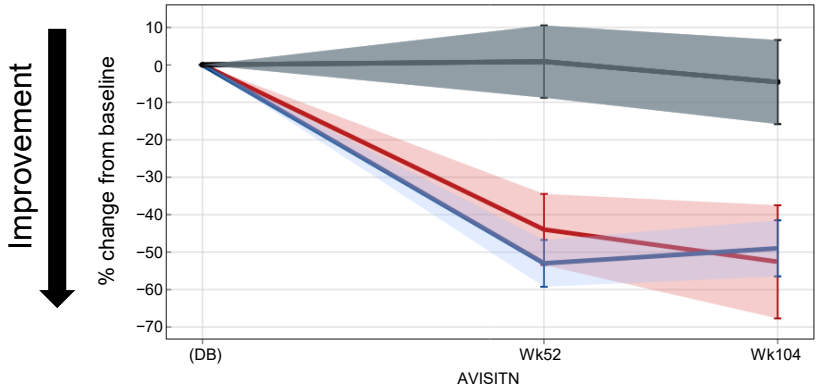
Week52 3000mg: -35.6±9.5

Percent change from baseline in CSF total tau



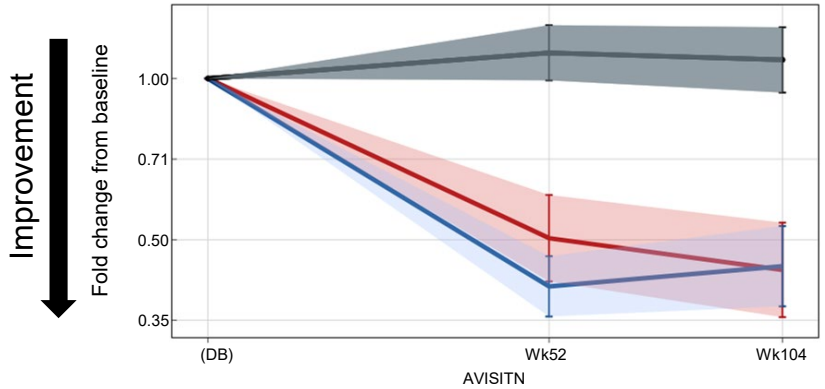
Week52 3000mg: -32.2±7.7

Percent change from baseline in CSF p-tau205



Week52 3000mg: -53.0±6.3

Fold change from baseline in CSF p-tau231



Week52 3000mg: -1.3±0.2

- p-tau217 (FREE and TOTAL) were reduced by 90 and 75%, respectively (shown previously)[1]
- Other p-tau markers reduced by 30-50%
  - Accumulated target engagement effect (since not seen as dramatically in acute treatment studies[2]) or pharmacodynamic effect?

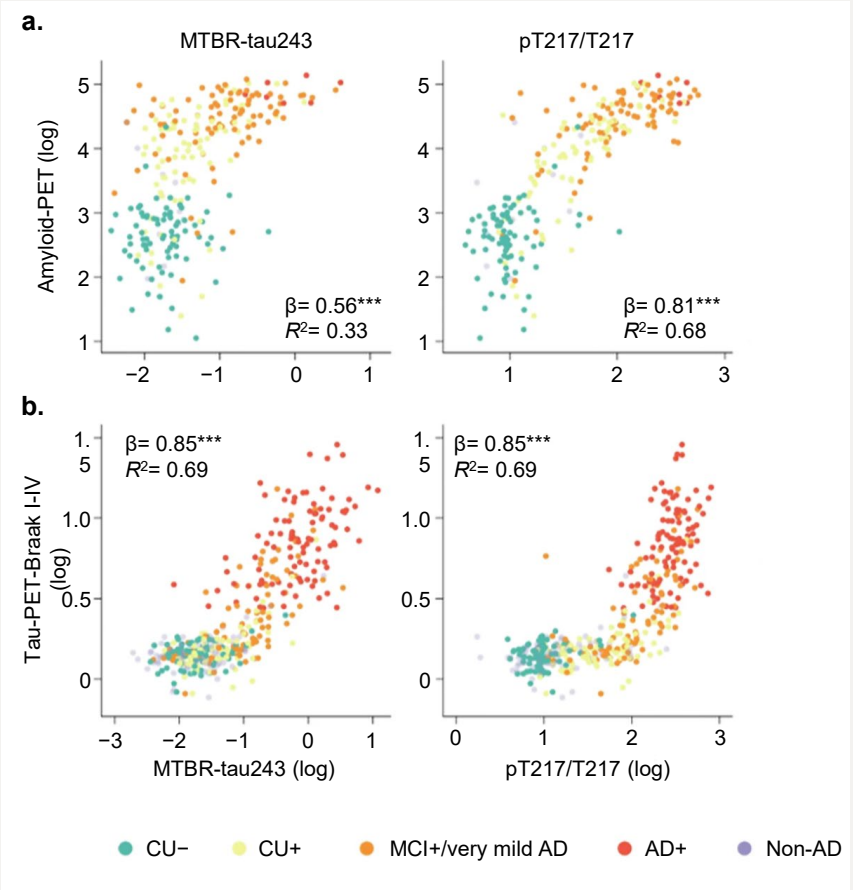
Treatment

- Placebo
- Posdinemab 1000 mg
- Posdinemab 3000 mg

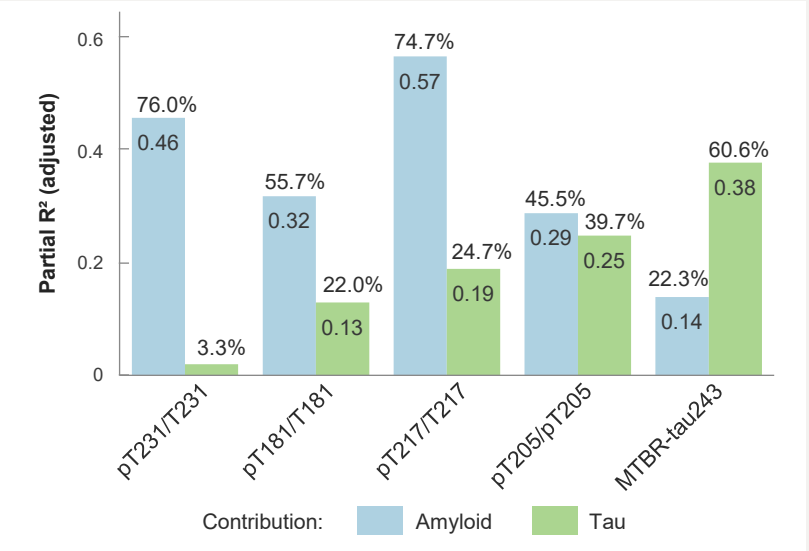
1. Cohen S, et al. Presented at: AD/PD 2026; March 17-21, 2026; Copenhagen, Denmark. 2. Galpern WR, et al. *J Prev Alzheimers Dis.* 2024;11(6):1592-1603. CSF, cerebrospinal fluid; p-tau, phosphorylated tau. Shading and error bars=95% confidence interval

CSF eMTBR243 may be a unique tau measure, best reflecting tau tangles

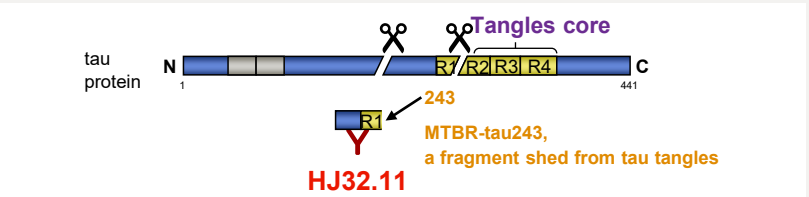
- p-tau217 associates best with amyloid burden[1]
- eMTBR243 associates best with tau burden[1]



eMTBR243 is unique in explaining variance in brain tau > amyloid[1]



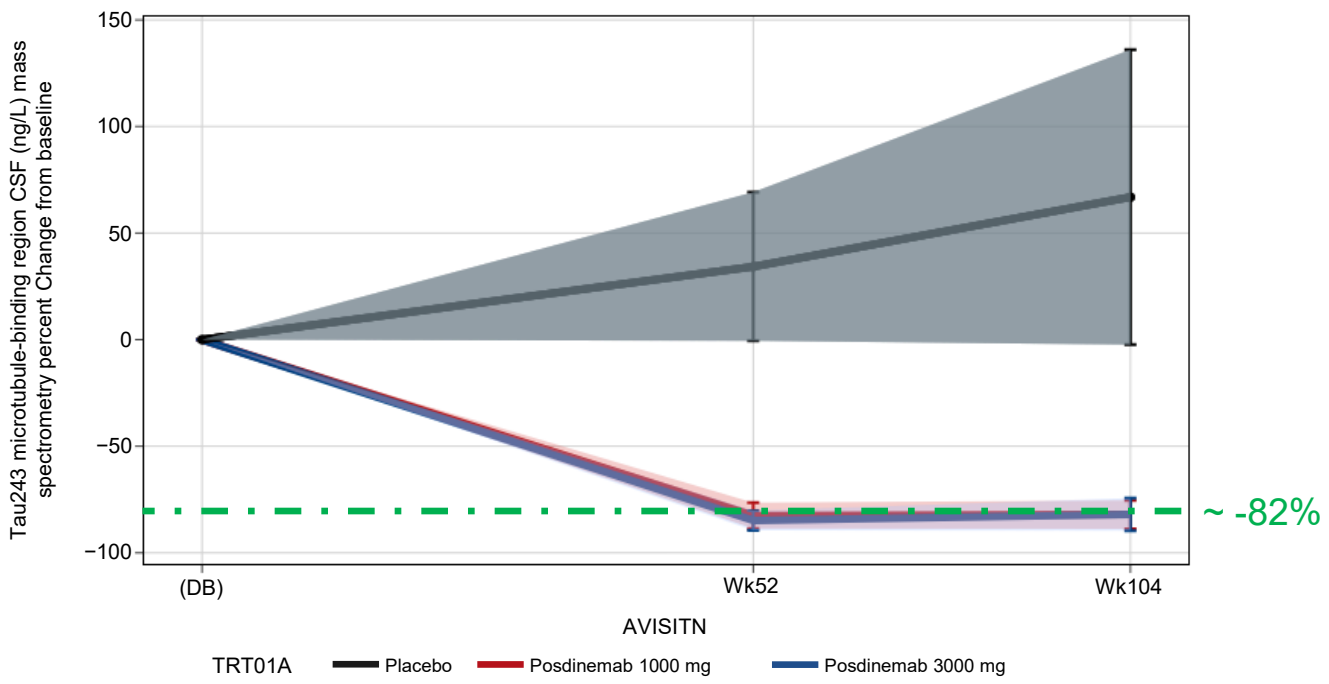
eMTBR243 is a fragment in the R1 MTBR region[1,2]



Figures adapted from Horie K, et al.[1,2]

eMTBR243 is currently only measurable by a proprietary mass spectrometry method (C2N). 1. Horie K, et al. *Nat Med.* 2023 Aug;29(8):1954-1963. 2. Horie K, et al. Presented at: AD/PD 2024; March 5-9, 2024; Lisbon, Portugal.
eMTBR, endogenous microtubule-binding region; p-tau, phosphorylated tau.

Results: Posdinemab reduced CSF eMTBR243 substantially (~82%)



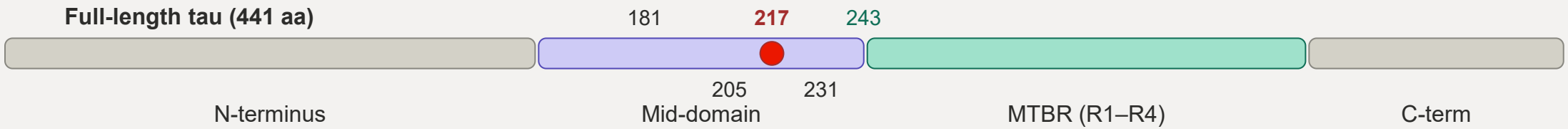
Shading and error bars=95% CI

- CSF eMTBR243 was reduced despite it being more associated with tau PET than other tau species in observational studies[1], and despite prominent cleavage on both sides of this epitope
  - Is this drug interference?
    - *No. In Vitro studies indicate no effect of spiked in posdinemab.*
  - Is this target engagement?
    - i.e. all parental eMTBR243 fragments connect to p217?
    - *Partially. In Vitro studies indicate very modest depletion by posdinemab.*
  - tau kinetics may provide additional information
    - *In the Phase 1 program with more frequent CSF sampling, non-p217 tau fragments dropped more slowly than p217 tau[2]*

1. Horie K, et al. *Nat Med.* 2023 Aug;29(8):1954-1963. 2. Galpern WR, et al. *J Prev Alzheimers Dis.* 2024;11(6):1592-1603. CI, confidence interval; CSF, cerebrospinal fluid; eMTBR, endogenous microtubule-binding region; PET, positron emission tomography.

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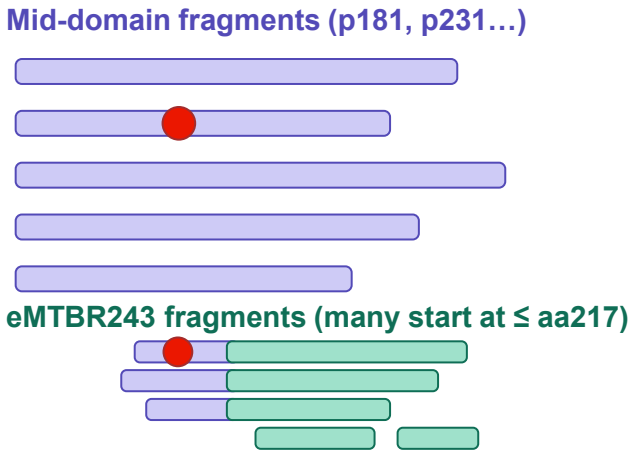
Proposed mechanism of posdinemab impact on p181, p205, p231, tTau, eMTBR243: accumulated target engagement (TE)



In CSF, tau is cut into many fragments

1. CSF fragment pool

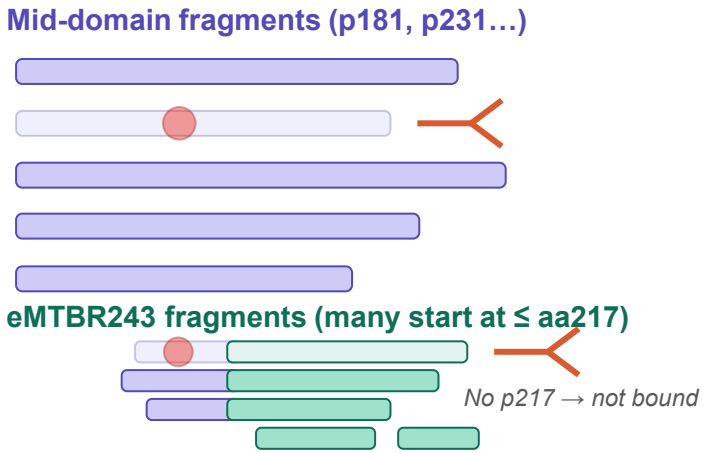
p217 is on only a minority of fragments



Concept adapted from Horie K, et al.[1]

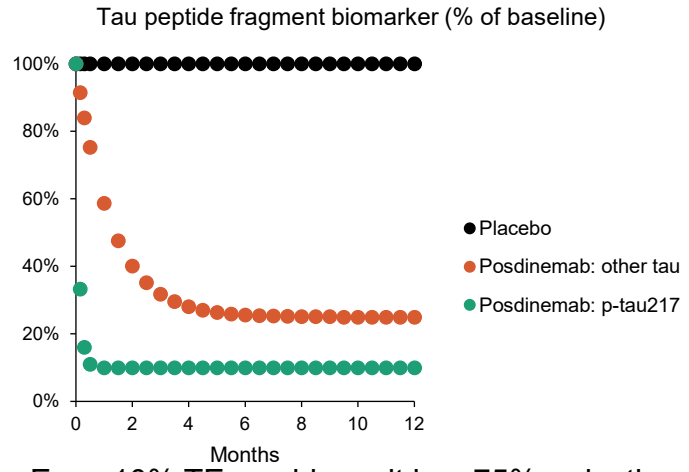
2. Posdinemab binds

only the p217-bearing fragments



Concept adapted from Courade JP, et al.[2]

3. Greater depletion over time



Even 10% TE would result in a 75% reduction in the biomarker by 1 year

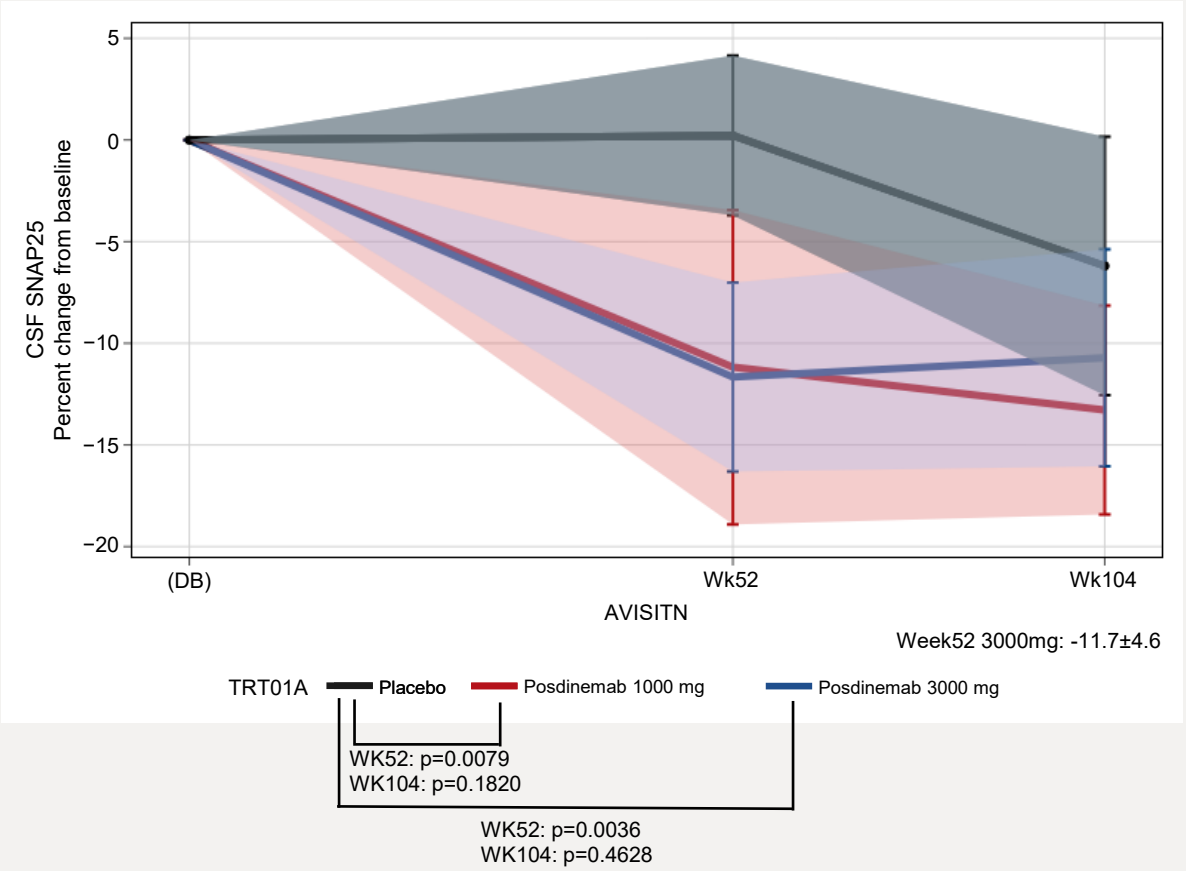
p217 (target) | Mid-domain fragments | MTBR fragments | Posdinemab

1. Horie K, et al. *Brain.* 2021 Mar 3;144(2):515-527. 2. Courade JP, et al. *Acta Neuropathol.* 2018 Nov;136(5):729-745. 3. Geerts H, et al. *Sci Rep.* 2023 Sep 1;13(1):14342. 4. Sato C, et al. *Neuron.* 2018 Mar 21;97(6):1284-1298.e7.
MTBR, microtubule-binding region; eMTBR, endogenous MTBR; t½, half-life; TE, target engagement.

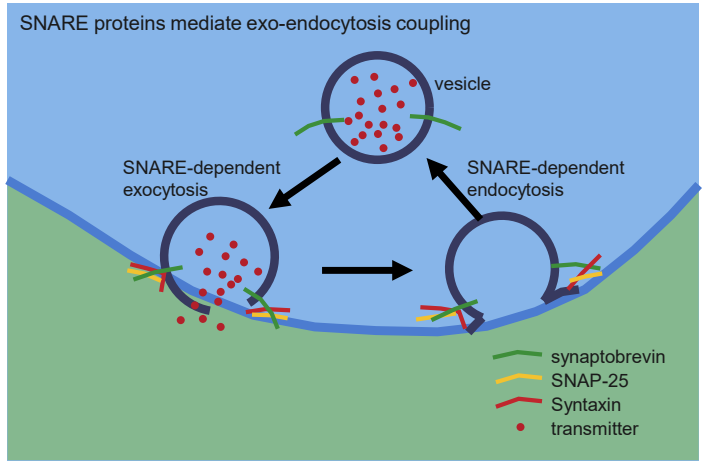
Presented by Gallen Triana-Baltzer at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Results: Posdinemab modestly reduced synaptic marker CSF SNAP25

% change in CSF Synaptosomal-Associated Protein 25 (Quanterix Simoa kit assay)

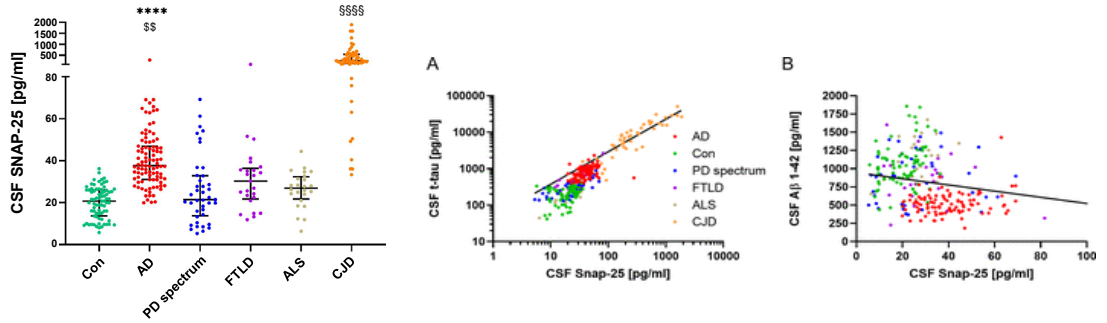


SNAP25 is part of the presynaptic vesicle release assembly



Adapted from Xu J, et al.[1]

SNAP25 is elevated in AD and correlates with A-T measures[2]



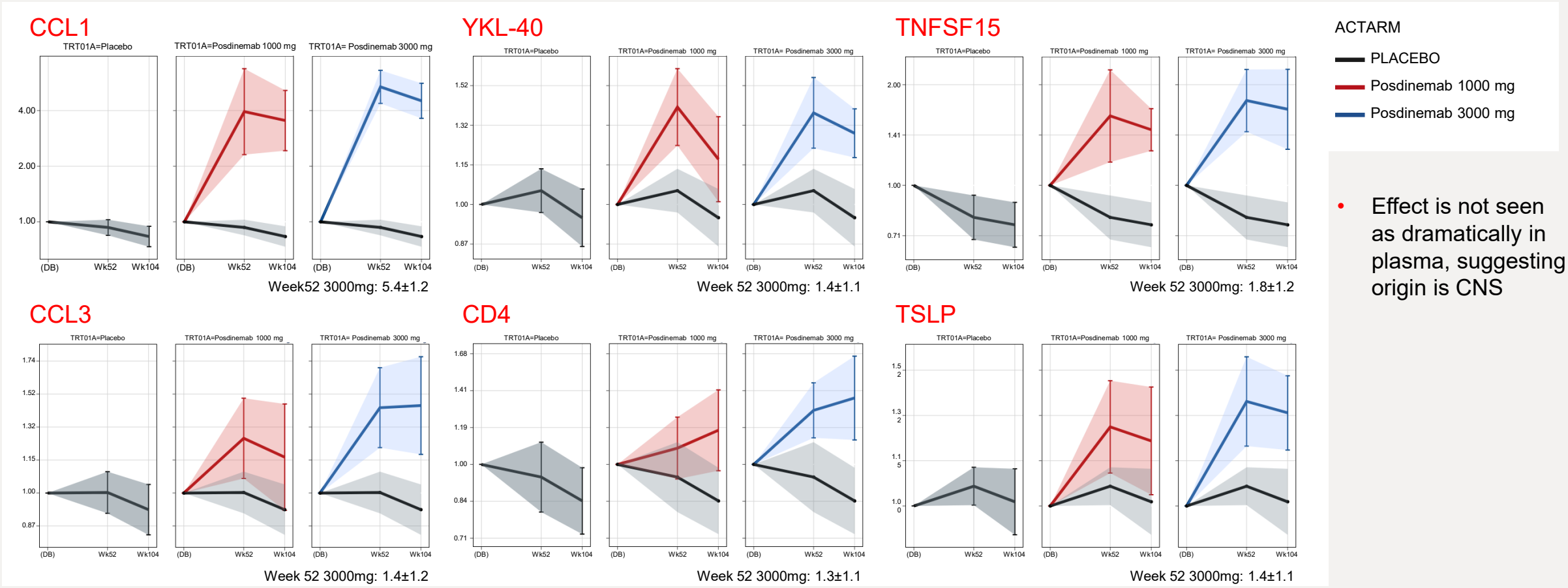
Adapted from Halbgebauer S, et al.[2]

1. Xu J, et al. *Cell Rep.* 2013 May 30;3(5):1414-1421. 2. Halbgebauer S, et al. *J Neurol Neurosurg Psychiatry*. 2022 Oct;93(10):1059-1065. AD, Alzheimer's disease; A-T, amyloid–tau; CSF, cerebrospinal fluid; SNAP25, synaptosomal-associated protein 25. Shading and error bars=95% confidence interval

Presented by Gallen Triana-Baltzer at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Results: Several inflammatory chemokines were upregulated by posdinemab

- CSF inflammatory markers as measured by NULISA panel



- Effect is not seen as dramatically in plasma, suggesting origin is CNS

Y-axis = log2 change in Normalized Protein Quantification (NPQ)

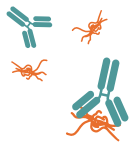
Error bars and bands represent 95% CI

CCL, C-C motif chemokine ligand; CD4, cluster of differentiation 4; CI, confidence interval; CNS, central nervous system; NPQ, normalized protein quantification; TNFSF15, TNF superfamily member 15; TSLP, thymic stromal lymphopoietin; YKL-40, chitinase-3-like protein 1.

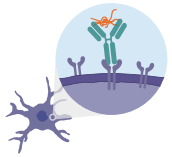
Presented by Gallen Triana-Baltzer at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Results: Posdinemab increased CSF inflammatory markers, more so in higher tau burden participants

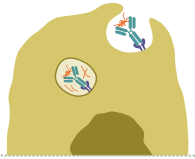
Proposed mechanism



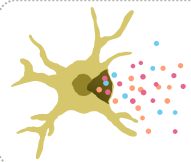
1. Posdinemab binds soluble tau, forming antibody–tau complexes



2. Glia recognize the complexes via the antibody Fc region[1]



3. Glia engulf the complex and become activated

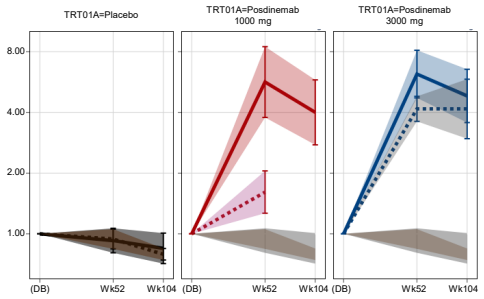


4. Cytokines and chemokines released (CCL1, CCL3, TNFSF15, TSLP…)

More tau → more complexes → larger response (solid vs dashed lines)

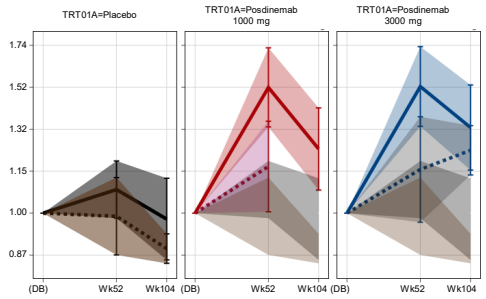
- Trend of dose response in low tau burden group

CCL1



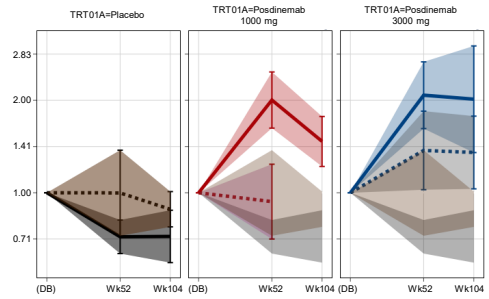
Wk52 3000HIGH: 6.2±1.3
Wk52 3000LOW: 4.2±1.2

YKL-40



Wk52 3000HIGH: 1.5±1.1
Wk52 3000LOW: 1.2±1.2

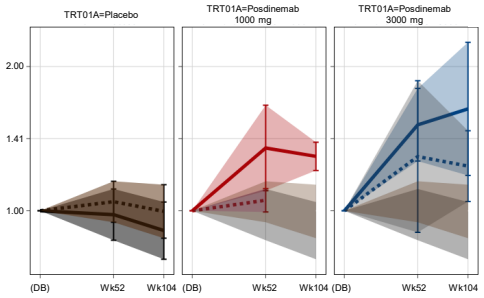
TNFSF15



Wk52 3000HIGH: 2.1±1.3
Wk52 3000LOW: 1.4±1.2

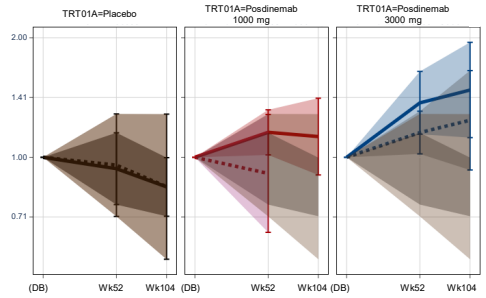
ACTARM
- Placebo
- Posdinemab 1000 mg
- Posdinemab 3000 mg

CCL3



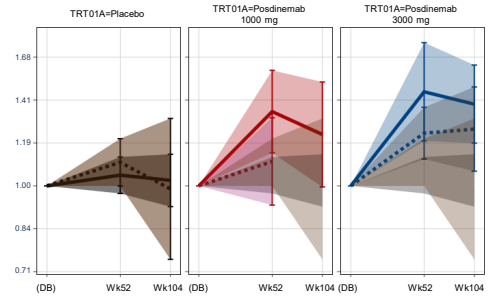
Wk52 3000HIGH: 1.5±1.2
Wk52 3000LOW: 1.3±1.4

CD4



Wk52 3000HIGH: 1.4±1.2
Wk52 3000LOW: 1.2±1.1

TSLP



Wk52 3000HIGH: 1.5±1.2
Wk52 3000LOW: 1.2±1.4

High tau burden – solid lines
Low tau burden – dashed lines

Y-axis = log2 change in Normalized Protein Quantification (NPQ).

Error bars and bands represent 95% CI

Mechanism panel is a schematic of a proposed mechanism; Fc-mediated microglial activation and uptake has been shown for the anti-amyloid antibody lecanemab [1]. 1. Albertini G, et al. *Nat Neurosci.* 2026 Jan;29(1):100-110. CCL, C-C motif chemokine ligand; CD4, cluster of differentiation 4; CI, confidence interval; CSF, cerebrospinal fluid; NPQ, normalized protein quantification; NULISA, nucleic acid-linked immuno-sandwich assay; TNFSF15, TNF superfamily member 15; TSLP, thymic stromal lymphopoietin; YKL-40, chitinase-3-like protein 1.

Presented by Gallen Triana-Baltzer at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Results: No significant impact of posdinemab on other amyloid, neurodegeneration, synaptic or co-pathology biomarkers

Analyte	Matrix	Change/trend?
p-tau205, BD tTau	Plasma	↑1.8x, ↑1.6x
Aβ40, Aβ42, Aβ42/40 ratio	CSF	No change
NfL	CSF	No change
NfL	Plasma	No change
GFAP	CSF	No change
GFAP	Plasma	No change
β-synuclein	CSF	No change
NRGN	CSF	No change
TREM2	CSF	No change
NPTX2	CSF	No change
sPDGFRβ	CSF	No change
α-synuclein, total & pS129	CSF	No change
TDP-43, total & pS409	CSF	No change
NULISA Inflam + CNS	CSF	227/276 analytes no change
NULISA Inflam + CNS	Plasma	320/366 analytes no change

Aβ, amyloid beta; BD, brain-derived; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; NPTX2, neuronal pentraxin 2; NRGN, neurogranin; p-tau, phosphorylated tau; sPDGFRβ, soluble platelet-derived growth factor receptor β; TDP-43, TAR DNA-binding protein 43; TREM2, triggering receptor expressed on myeloid cells 2; tTau, total tau.

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Conclusions: Summary of fluid biomarker results

- **Robust surrogate target engagement:** CSF p217+tau reductions. Sufficient posdinemab–tau engagement in CSF; engagement in the synaptic cleft remains unknown
- **Probable accumulated target engagement (over 1 year):** CSF tTau, p-tau181, p-tau205, p-tau231 and eMTBR243 reductions. NOT indicative of an impact on pathology or clinical efficacy
- **Probable pharmacodynamic changes:** CSF SNAP25 reductions, but no other neurodegeneration/synaptic markers; CSF inflammation increases, which may reflect posdinemab–brain tau complexes recognized by microglia; impact unknown
- **Overall:** despite reductions in CSF p-tau217 indicating robust target engagement in CSF, no clinical efficacy was observed; posdinemab may not have impacted pathology sufficiently or appropriately

CSF, cerebrospinal fluid; eMTBR, endogenous microtubule-binding region; p-tau, phosphorylated tau; SNAP25, synaptosomal-associated protein 25; tTau, total tau.

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So What? Learnings from the Autonomy Phase 2 clinical trial

Patient selection

Plasma p-tau217 is a low-friction tool that helps enroll a plasma T+, amyloid-positive population. Combined with CDR-GS of 0.5, this enriches for tau PET-positivity.

Biomarkers reveal mechanism

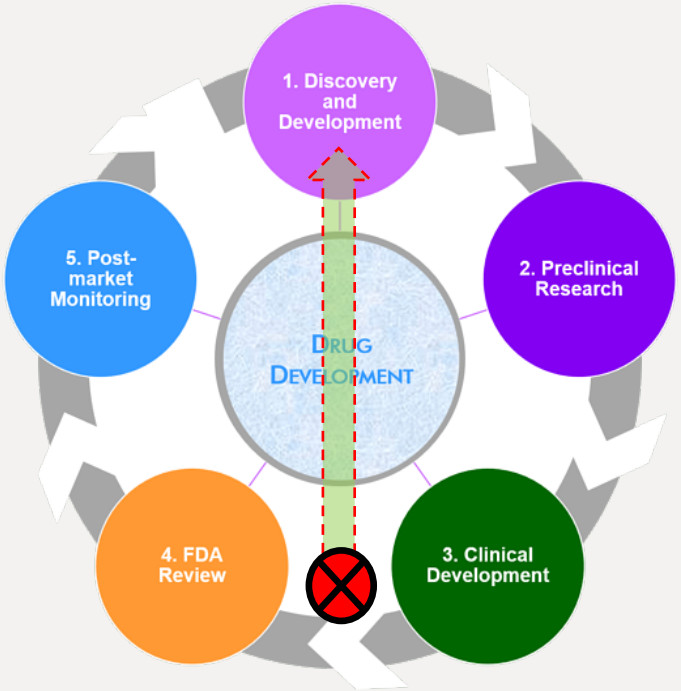
Cognition and PK alone would have left us relatively blind to the treatment effect on AD pathology. Fluid biomarker and imaging data are helpful in understanding MOA.

Measure closer to pathology

Posdinemab did not substantially impact cognition or tau PET, yet soluble tau markers were impacted substantially.

Inflammation

Posdinemab may have had a chronic inflammatory effect.



AD, Alzheimer's disease; CDR-GS, Clinical Dementia Rating–Global Score; MOA, mechanism of action; PET, positron emission tomography; PK, pharmacokinetics.

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